

Claims

1. A pharmaceutical composition comprising at least one TGF-beta antagonist, selected from the group of

- oligonucleotides hybridising with an area of the messenger RNA (m-RNA) and/or DNA encoding TGF-beta,
- TGF-beta receptors and/or parts of them binding TGF-beta,
- proteins, except antibodies, inhibiting TGF-beta
- peptides of less than 100 kDa inhibiting TGF-beta
- peptides being parts of TGF-beta

and at least one substance inhibiting cell proliferation and/or inducing cell death, selected from the group of

temozolomide, nitrosoureas, Vinca alkaloids, antagonists of the purine and pyrimidine bases, cytostatic active antibiotics, caphthotecine derivatives, anti-androgens, anti-estrogens, anti-progesterons and analogs of gonadotropin releasing hormon.

2. The pharmaceutical composition of claim 1 wherein the at least one TGF-beta antagonist and the at least one substance inhibiting cell proliferation and/or inducing cell death are mixed together.

3. The pharmaceutical composition of claim 1 wherein the at least one TGF-beta antagonist and the at least one substance inhibiting cell proliferation and/or inducing cell death are separate.

4. The pharmaceutical composition according to claim 1 to 3, wherein the oligonucleotide comprises at least one of the sequences with Seq. ID. No. 1-146 identified in the sequence listing.

5. The pharmaceutical composition according to claim 4 wherein at least one nucleotide of the oligonucleotide is modified at the sugar moiety, the base and/or the internucleotide linkage.

6. The pharmaceutical composition according to claim 5 wherein at least one modified internucleotide linkage is a phosphorothioate linkage.

7. The pharmaceutical composition according to claim 1 to 6 wherein

- the nitrosourea is selected from the group of ACNU, BCNU and CCNU,
- the Vinca-alcaloid is selected from the group of vinblastine, vincristine, vindesine,
- the antagonist of the purine and pyrimidine bases is selected from the group of 5-fluorouracile, 5-fluorodeoxyuridine, cytarabine and gemcitabine,
- the cytostatic antibiotic is selected from the group of doxorubicine and liposomal PEGylated doxorubicin,
- the camphthotecine derivative is selected from the group of irinotecane and topotecane,
- the anti estrogens are selected from the group of tamoxifen, exemestane, anastrozole and fulvestrant,
- the antiandrogens are selected from the group of flutamide and bicalutamide,

- the antiprogesterons are selected from the group of mifepriston
- the analogs of gonadotropin releasing hormon are selected from the group of leuprolide and gosereline.

8. A pharmaceutical composition comprising at least one stimulator of the function of the immune system and/or immune cells and at least one substance inhibiting the cell proliferation and/or inducing cell death.

9. The pharmaceutical composition of claim 8 wherein the at least one stimulator of the function of the immune system and/or immune cells and the at least one substance inhibiting cell proliferation and/or inducing cell death are separate.

10. The pharmaceutical composition of claim 9 wherein the at least one stimulator of the function of the immune system and/or immune cells and the at least one substance inhibiting cell proliferation and/or inducing cell death are mixed together.

11. The pharmaceutical composition according to one of the claims 8 to 10, wherein the at least one stimulator of the function of the immune system and/or the immune cells is

- stimulating and/or enhancing the synthesis and/or the function of cytokines such as GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotatic proteins (MCP-1), lymphotactin, interleukin-2, interleukin-4, interleukin-6, interleukin-12, interleukin-18 and/or interferon gamma or is one of these cytokines,
- selected from the group consisting of viruses, viral antigens, antigens expressed in tumor cells or pathogens, but not in normal cells, organ specific antigens expressed in affected organs which are not essential for the organism, fusion cells of dendritic cells and tumor cells and dendritic cells itself

- an antagonist of factors negatively influencing the function of the immune system or a vaccine.

and

- the at least one substance inhibiting cell proliferation and/or inducing cell death is an antineoplastic chemotherapeutic agent.

12. The pharmaceutical composition according to claim 11 wherein the antagonist of factors negatively influencing the function of the immune system is selected from the group of DNA- or RNA-fragments, antisense oligonucleotides, their active derivatives, antibodies, parts of antibodies, proteins, receptors, parts of receptors, peptides and molecules of less than 10,000 Da.

13. The pharmaceutical composition according to claim 12 wherein the antisense oligonucleotide is an oligonucleotide hybridising with an area of the messenger RNA (mRNA) and/or DNA encoding TGF-beta, VEGF, PGE2 or IL-10 and/or their receptors.

14. Use of a composition comprising at least one TGF-beta antagonist, selected from the group of

oligonucleotides hybridising with an area of the messenger RNA (m-RNA) and/or DNA encoding TGF-beta,

- TGF-beta receptors and/or parts of them binding TGF-beta,
- proteins, except antibodies, inhibiting TGF-beta
- peptides of less than 100 kDa inhibiting TGF-beta
- peptides being parts of TGF-beta

and

- at least one substance inhibiting cell proliferation and/or inducing cell death, selected from the group of

temozolomid, nitrosoureas, Vinca alkaloids, antagonists of the purine and pyrimidine bases, cytostatic active antibiotics, capthotecine derivatives, anti-estrogens, anti-androgens and analogs of gonadotropin releasing hormon.

for the preparation of a pharmaceutical composition for the treatment of neoplasms.

15. Use of a composition comprising at least one stimulator of the function of the immune system and/or or immune cells and at least one substance inhibiting the cell proliferation and/or inducing cell death for the preparation of a pharmaceutical composition for the treatment of neoplasms.

16. Use according to claim 14 or 15 for the treatment of neoplasms selected from the group of solid tumors; blood born tumors such as leukemias, acute or chronic myelotic or lymphoblastic leukemia; tumor metastasis; benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; pre-malignant tumors; astrocytoma, blastoma, chordoma, craniopharyngioma, ependymoma, Ewing's tumor, germinoma, glioma, glioblastoma, hemangioblastoma, hemangiopericytoma, Hodgkins lymphoma, medulloblastoma, leukaemia, mesothelioma, neuroblastoma, non-Hodgkins lymphoma, pinealoma, retinoblastoma, sarcoma (including angiosarcoma, chondrosarcoma, endothelial sarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, lymphangioendotheliosarcoma, lymphangiosarcoma, medulloblastoma, melanoma, meningioma, myosarcoma, neurinoma, oligodendroglioma, osteogenic sarcoma, osteosarcoma), seminoma, subependymoma, Wilm's tumor, or is selected from the group of bile duct carcinoma, bladder carcinoma, brain tumor, breast carcinoma, bronchogenic carcinoma, carcinoma of the kidney, cervical carcinoma, choriocarcinoma, cystadenocarcinoma, embryonal carcinoma, epithelial carcinoma, esophageal carcinoma, cervical carcinoma, colon carcinoma, colorectal carcinoma, endometrial carcinoma, gallbladder carcinoma, gastric carcinoma, head and neck carcinoma, liver carcinoma, lung carcinoma, medullary carcinoma, non-small cell bronchogenic/lung carcinoma, ovarian carcinoma, pancreas carcinoma, papillary carcinoma, papillary adenocarcinoma, prostate carcinoma, small intestine carcinoma, rectal carcinoma, renal cell carcinoma, skin carcinoma, small-cell bronchogenic/lung carcinoma, squamous cell carcinoma, sebaceous gland carcinoma, testicular carcinoma, uterine carcinoma.

17. Use according to claim 15 or 16 for the for the treatment of glioma, glioblastoma and/or anaplastic astrocytoma.

18. Method of treating neoplasms comprising the step of administering at least one TGF-beta antagonist in combination with

at least one substance inhibiting the cell proliferation and/or inducing cell death and/or the step of applying radiation.

19. Method of treating neoplasms comprising the step of administering at least one stimulator of the function of the immune system and/or or immune cells in combination with

at least one substance inhibiting the cell proliferation and/or inducing cell death and/or the step of applying radiation.

20. Method of treating neoplasms according to claim 18 or 19 wherein the neoplasm is selected from the group of: bil duct carcinoma, bladder carcinoma, brain tumor, breast carcinoma, bronchogenic carcinoma, carcinoma of the kidney, cervical carcinoma, choriocarcinoma, cystadenocarcinome, embrional carcinoma, epithelial carcinoma, esophageal carcinoma, cervical carcinoma, colon carcinoma, colorectal carcinoma, endometrial carcinoma, gallbladder carcinoma, gastric carcinoma, head carcinoma, liver carcinoma, lung carcinoma, medullary carcinoma, neck carcinoma, non-small-cell bronchogenic/lung carcinoma, ovarian carcinoma, pancreas carcinoma, papillary carcinoma, papillary adenocarcinoma, prostata carcinoma, small intestine carcinoma, prostate carcinoma, rectal carcinoma, renal cell carcinoma, skin carcinoma, small-cell bronchogenic/lung carcinoma, squamous cell carcinoma, sebaceous gland carcinoma, testicular carcinoma, uterine carcinoma, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; pre-malignant tumors; rheumatoid arthritis; psoriasis; astracytoma, acoustic neuroma, blastoma, Ewing's tumor, astracytoma, craniopharyngloma, ependymoma, medulloblastoma, glioma, hemangloblastoma, Hodgkins-lymphoma, medullablastoma, leukaemia, mesothelioma, neuroblastoma, neurofibroma, non-Hodgkins lymphoma, pinealoma, retinoblastoma, retinoblastoma, sarcoma (including angiosarcoma, chondrosarcoma, endothelialsarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, lymphangioandotheliosarcoma, lyphangiosarcoma, melanoma, meningioma, myosarcoma, oligodendroglioma, osteogenic sarcoma, osteosarcoma), seminoma, trachomas, Wilm's tumor.

21. Method of treating neoplasms according to claim 18 or 19 wherein the step of administering an pharmaceutical composition is before or after applying radiation.
22. Method of treating neoplasms according to claim 18 or 19 wherein the step of administering a pharmaceutical composition is together with applying radiation.
23. Method of treating neoplasms according to claim 21 or 22 wherein the total amount of radiation within one cycle is from about 10 Gy to about 100 Gy.
25. Method of treating neoplasms according to claim 23 wherein the total amount of radiation of one cycle is applied by several fractions from of about 1 Gy to about 2 Gy.
26. Peptides comprising from about 5 to about 50 of the amino acids of the protein selected from the group of TGF-beta1, TGF-beta2 and/or TGF-beta3 and their conservative analogs.
27. Pharmaceutical composition comprising peptides comprising from about 5 to about 50 of the amino acids of the protein selected from the group of TGF-beta1, TGF-beta2 and/or TGF-beta3 and their conservative analogs.
28. Use of peptides comprising from about 5 to about 50 amino acids of the protein selected from the group of TGF-beta1, TGF-beta2 and/or TGF-beta 3 and their conservative analogs for the treatment of neoplasms.

29. Method of treating neoplasms by using peptides comprising from about 5 to about 50 amino acids of the protein selected from the group of TGF-beta1, TGf-beta2 and/or TGF-beta3 and their analogs.